Webinar: **Genomic Profiling and the Future of Early Breast Cancer Care**

IEO European Institute of Oncology

Building consensus and future directions on clinical utility of genomic expression profiles

Giuseppe Curigliano
European Institute of Oncology
University of Milano, Milano, Italy

prosigna® Breast cancer gene signature assay

veracyte

Cancer Detection during COVID-19 Pandemic

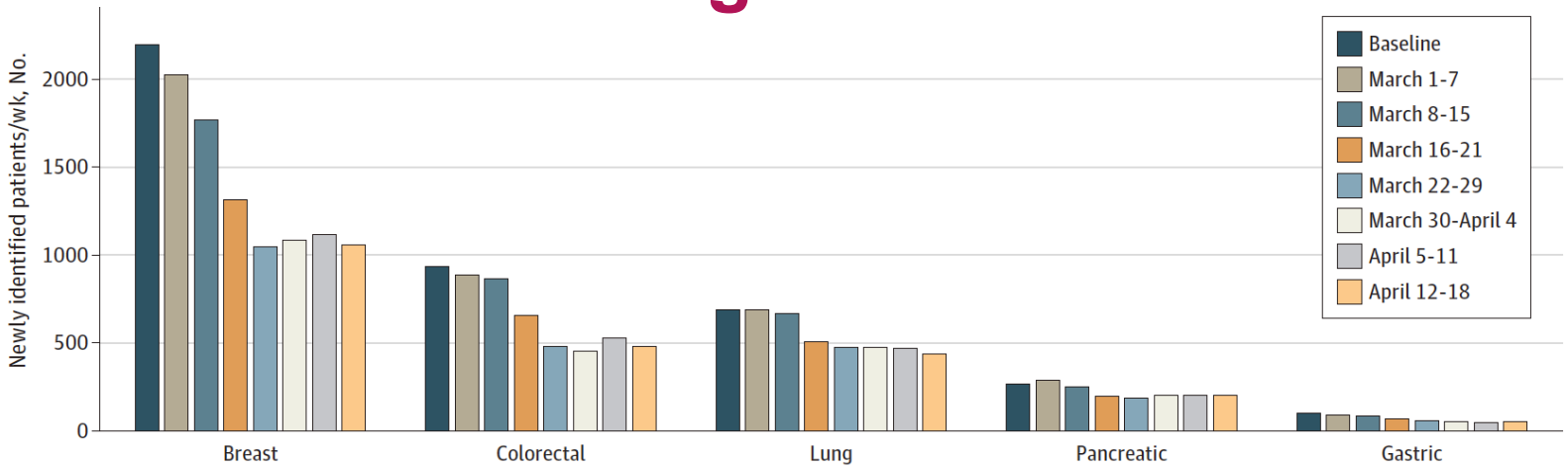


Table. Demographic Information for Patients With Newly Identified Cancer

	January 6, 2019, to February 29, 2020			March 1 to April 18, 2020		
Cancer type	Patients, No.	Women, No. (%)	Age, mean (SD), y	Patients, No.	Women, No. (%)	Age, mean (SD), y
Breast	132 513	132 513 (100)	64.3 (12.7)	9475	9475 (100)	63.0 (13.0)
Colorectal	56 744	28 056 (49.6)	66.7 (13.4)	4377	2109 (48.2)	65.4 (13.3)

JAMA Network Open. 2020;3(8):e2017267. doi:10.1001/jamanetworkopen.2020.17267

prosigna® Breast cancer gene signature assay

veracyte

Managing cancer patients during the COVID-19 pandemic: An ESMO Interdisciplinary Expert Consensus

Breast Cancer:

STATEMENT 18: For breast cancer patients in the curative setting, regimens and doses of adjuvant/neoadjuvant systemic therapies should be followed, always preceded by a multidisciplinary discussion, risk/benefit analysis and discussion with the patient. … Some types of adjuvant/neoadjuvant systemic therapies are not, in principle, associated with risk of complications of COVID-19 and should therefore be used as recommended by the guidelines, in particular, anti-HER2 and endocrine therapies.

In situations where the risk/benefit of adjuvant/neoadjuvant systemic chemotherapy is controversial or uncertain, it may be wiser to decide against that treatment during the COVID-19 pandemic, always after careful discussion with the patient (42).

Curigliano G et al. Ann Oncol. 2020 Jul 29:S0923-7534(20)39948-8.

Evidence in Node Positive Disease
- The Danish Populational Cohort (DBCG)

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor–Positive Early Breast Cancer

Anne-Vibeke Lænkholm, Maj-Britt Jensen, Jens Ole Eriksen, Birgitte Bruun Rasmussen, Ann S. Knoop, Wesley Buckingham, Sean Ferree, Carl Schaper, Torsten O. Nielsen, Taryn Haffner, Torben Kibøl, Maj-Lis Møller Talman, Anne Marie Bak Jylling, Tomasz Piotr Tabor, and Bent Ejlertsen

Laenkholm AV *et al*. J Clin Oncol. 2018 Mar 10;36(8):735-740

prosigna® Breast cancer gene signature assay

veracyte

Evidence in node positive disease from Danish patient cohort (DBCG)

2,558 Patients ER+/HER2- Treated with 5y of Endocrine Therapy Alone

- **All breast cancer patients in Denmark from 2000-2003**
- **Over 50 years of age**
- **With one of the following risk factors**
  - Tumor size > 2cm
  - 1-3 positive lymph nodes
  - Ductal grade 2 or 3
- **Were allocated to 5 years of endocrine therapy alone and included in the study**

Parameter	N	(%)	Parameter	N	(%)
Age at diagnosis			**Histological Subtype**		
50-59	939	37%	Ductal	2126	83%
60-69	1082	42%	Lobular	340	13%
≥ 70	537	21%	Others	92	4%
Number of positive lymph nodes			**Malignancy Grade**		
0	1163	46%	I	628	25%
1	779	30%	II	1362	53%
2	393	15%	III	306	12%
3	223	9%	Unknown	262	10%
Tumor Size (mm)			**Lymphovascular invasion**		
≤ 10	241	9%	Present	280	11%
11-20	1087	43%	Absent	2278	89%
21-30	862	34%	**ER expression level**		
> 30	368	14%	10 – 59%	259	10%
Histological Subtype			60 – 89%	529	21%
Ductal	2126	83%	90 – 99%	674	26%
Lobular	340	13%	100%	1064	42%
Others	92	4%	Positive	32	1%

Laenkholm AV *et al*. J Clin Oncol. 2018 Mar 10;36(8):735-740

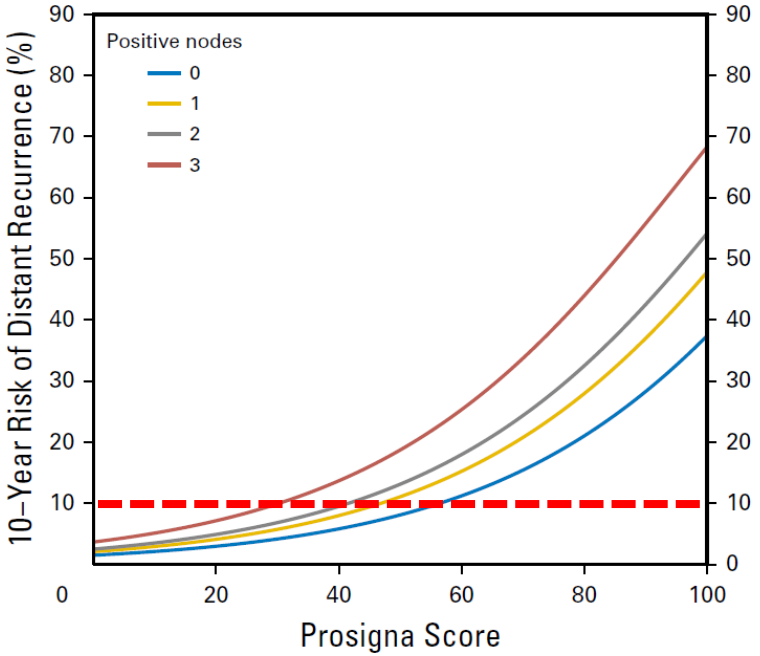
prosigna® Breast cancer gene signature assay

veracyte

Evidence in node positive disease from Danish patient cohort (DBCG)

Risk curves tailored to nodal status (0-3 positive nodes)

- **Risk curves from DBCG Cohort with increasing nodal burden**
- **Low risk patients identified with up to 3 positive lymph nodes (<10% risk of distant recurrence)**
- **Strongest evidence to date supporting potential for therapy de-escalation within node positive patients**



Laenkholm AV *et al*. J Clin Oncol. 2018 Mar 10;36(8):735-740

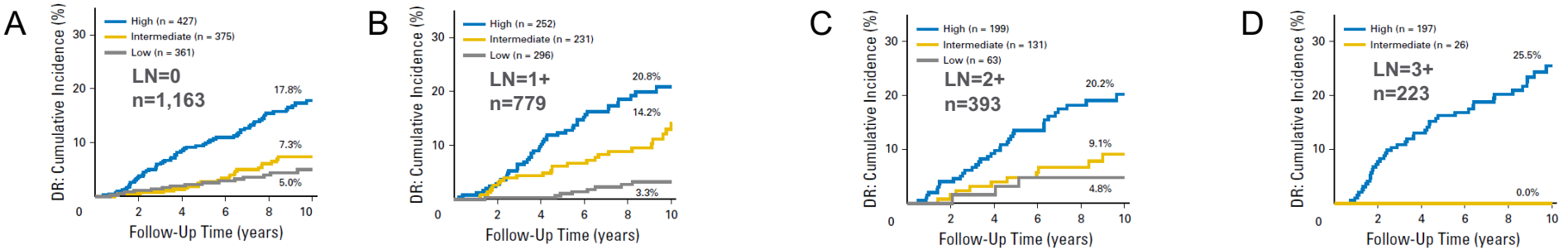
prosigna® Breast cancer gene signature assay

veracyte

DBCG - Distant recurrence risk at 10 years after 5 years of endocrine therapy alone

	Node Negative (n=1163)	Node Positive (n=1395)
Low risk	5% (95% CI, 2.9% to 8.0%)	3.5% (95% CI, 1.9% to 6.1%)
Intermediate risk	7.3%(95%CI, 4.8%to 10.5%)	11.5% (95% CI, 8.0% to 15.6%)
High risk	17.8% (95%CI, 14.9% to 22.4%)	22.1% (95% CI, 18.6% to 25.8%)

All patients categorized as low risk regardless of nodal involvement status had DR absolute risk below or equal to 5%



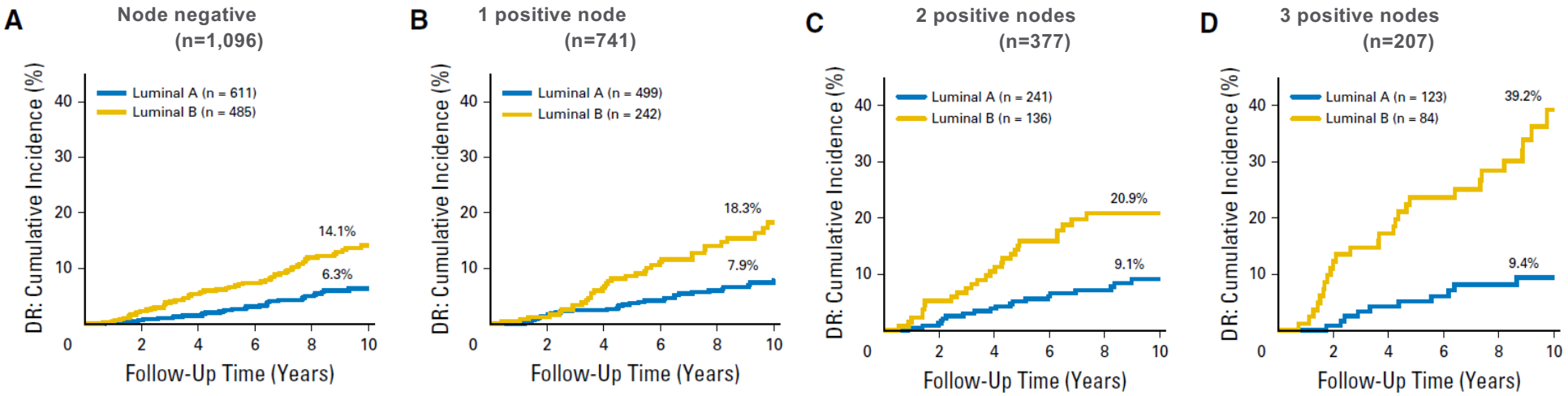
Laenkhollm AV *et al*. J Clin Oncol. 2018 Mar 10;36(8):735-740

prosigna® Breast cancer gene signature assay

veracyte

DBCG - Cumulative incidence by subtype

Regardless of nodal status, Luminal B tumors (n=947 pts) had a significantly worse outcome than Luminal A tumors (n=1,474 pts) **18.4% vs 7.6% risk of DR, respectively**



Laenkhollm AV *et al*. J Clin Oncol. 2018 Mar 10;36(8):735-740

prosigna® Breast cancer gene signature assay

veracyte

Major Prospective Studies of Biomarker Based Tests for HR+ Early Breast Cancer

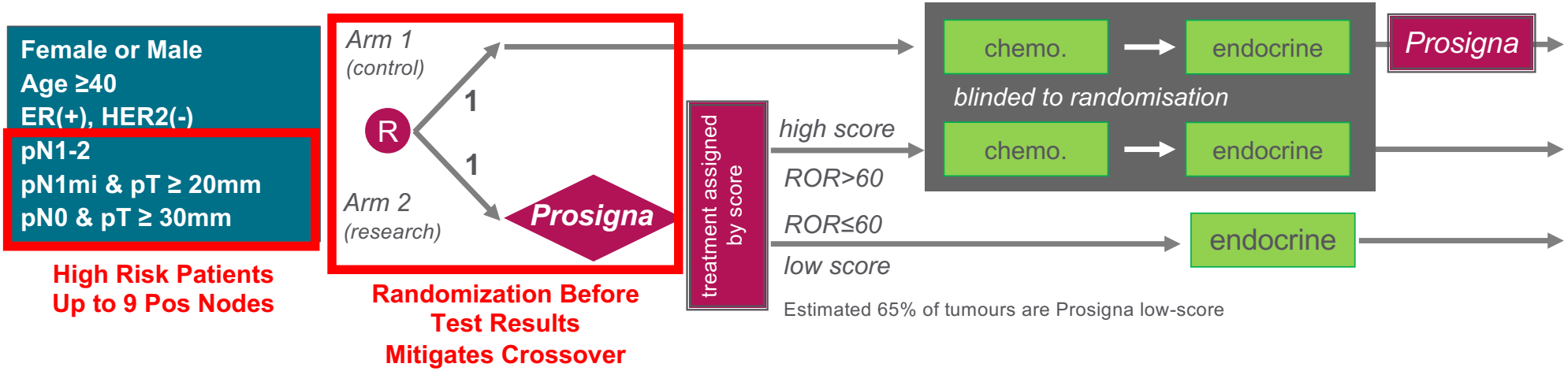
- **MammaPrint by Agendia**
  - MINDACT[1] – N0 and N1 Patients, Discordant Genomic and Clinical Risk Patients Randomized to CT
- **OncotypeDX by Exact Sciences**
  - TAILORx[2] – N0 Patients, RS 11-25 Randomized to CT
  - RxPonder[3] – N1 Patients, RS 0-25 Randomized to CT
- **Prosigna (PAM50) by NanoString**
  - OPTIMA[4] – N0, N1, and N2 Patients, All Patients Randomized to Test-Directed CT (CT for ROR > 60)
  - EXPERT[5] – N0 Patients, Low Risk Scores Randomized to Radiation Therapy (ROR ≤40)
- **EndoPredict by Myriad Genetics**
  - RESCUE[6] – N0 and N1 Patients, Low Risk Score Survival Observed (No Randomization to Therapy)

1. Cardoso F, et al. N Engl J Med 2016; 375: 717-729. 2. Sparano et al. N Engl J Med 2018 Jul 12;379(2):111-121. 3. J Natl Compr Canc Netw. 2017 Apr;15(4):494-503. 4. Bartlett JM et al, J Natl Cancer Inst. 2016 Apr 29;108(9). 5. ANZ 1601: EXPERT https://www.breastcancertrials.org.au/current-clinical-trials/expert. 6. Reaching for Evidence-baSed Chemotherapy Use in Endocrine Sensitive Breast Cancer (RESCUE) NCT03503799

prosigna® Breast cancer gene signature assay

veracyte.

OPTIMA Study Design Includes Prosigna to assess test-directed utility in higher-risk patients



1° Outcome =	Non-inferiority of IDFS (Δ = -3%, control arm 5yr IDFS 85% : HR 1.22) Cost effectiveness evaluation of test-directed treatment
2° Outcome =	Non-inferiority of IDFS in low-score patients (Δ=-3.5%)

Sample size = 4500 patients (+ OPTIMA prelim) Recruitment period = 60 months

Bartlett J *et al.* Clin Oncol (R Coll Radiol). 2013 Feb;25(2):109-16

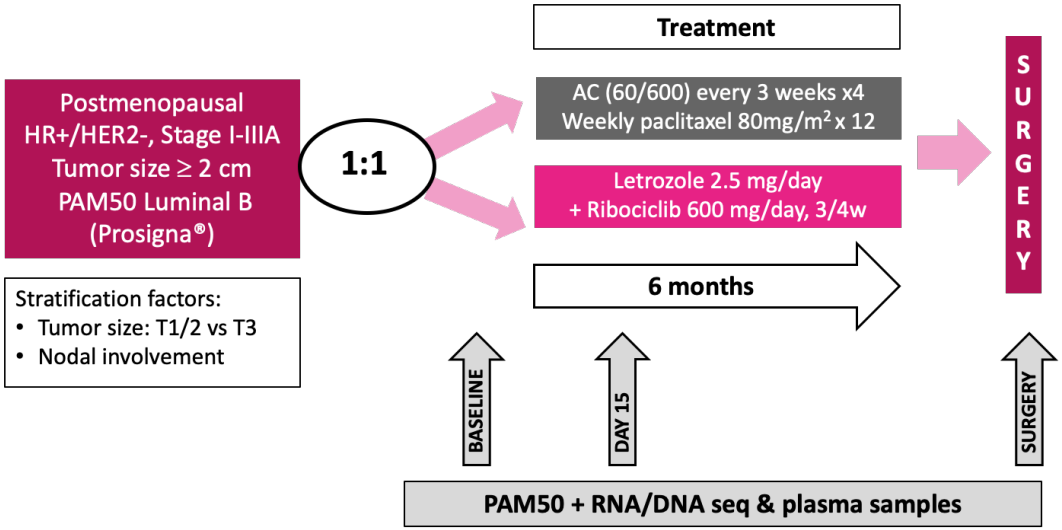
prosigna® Breast cancer gene signature assay

optima personalised treatment of breast cancer

Future directions on Prosigna/PAM50 clinical utility - Neoadjuvant setting

Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial

Aleix Prat, Cristina Saura, Tomás Pascual, Cristina Hernando, Montserrat Muñoz, Laia Paré, Blanca González Farré, Pedro L Fernández, Patricia Galván, Núria Chic, Xavier González Farré, Mafalda Oliveira, Miguel Gil-Gil, Miriam Arumi, Neus Ferrer, Alvaro Montaño, Yann Izarzugaza, Antonio Llombart-Cussac, Raquel Bratos, Santiago González Santiago, Eduardo Martínez, Sergio Hoyos, Beatriz Rojas, Juan Antonio Virizuela, Vanesa Ortega, Rafael López, Pamela Céliz, Eva Ciruelos, Patricia Villagrasa, Joaquín Gavilá



Prat A *et al*. Lancet Oncol. 2020 Jan;21(1):33-43

prosigna® Breast cancer gene signature assay

veracyte

CORALLEEN Study –
Patient Baseline Characteristics

	Ribociclib and letrozole group (n=52)	Chemotherapy group (n=54)
Median age, years	63.6 (56.5 – 70.3)	64.0 (58.3 – 71.8)
Tumour size		
T1	3 (6%)	3 (6%)
T2	40 (77%)	43 (80%)
T3	9 (17%)	8 (15%)
Lymph node status		
N0	31 (60%)	31 (57%)
N1	19 (37%)	22 (41%)
N2	2 (4%)	1 (2%)
Clinical baseline tumour stage		
I	2 (4%)	2 (4%)
II	43 (83%)	45 (83%)
III	7 (14%)	7 (13%)
Histological type		
Ductal	41 (79%)	48 (89%)
Lobular	10 (19%)	6 (11%)
Other	1 (2%)	0
Data are median (IQR), n (%), and mean (SD)		

	Ribociclib and letrozole group (n=52)	Chemotherapy group (n=54)
Median age, years	63.6 (56.5 – 70.3)	64.0 (58.3 – 71.8)
Progesterone receptor expression		
Progesterone receptor expression < 20%	18 (35%)	16 (30%)
Progesterone receptor expression negative	11 (21%)	9 (17%)
Ki67 expression (local)		
Median proportion of cells with Ki67 in a sample	30.0% (21.8 - 40.0)	35.0% (27.0 - 40.0)
Mean proportion of cells with Ki67 in a sample	31.1% (13.6)	35.2% (12.6)
≤14%	3 (6%)	2 (4%)
>14%	49 (94%)	51 (94%)
Missing	0	1 (2%)
PROSIGNA		
Median ROR score	70.0 (64.6 – 80.3)	77.0 (66.6 – 82.0)
Mean ROR score	71.5 (9.9)	74.2 (10.7)
ROR risk class		
Intermediate	8 (15%)	6 (11%)
High	44 (85%)	48 (89%)
Data are median (IQR), n (%), and mean (SD)		

Prat A *et al*. Lancet Oncol. 2020 Jan;21(1):33-43

prosigna® Breast cancer gene signature assay

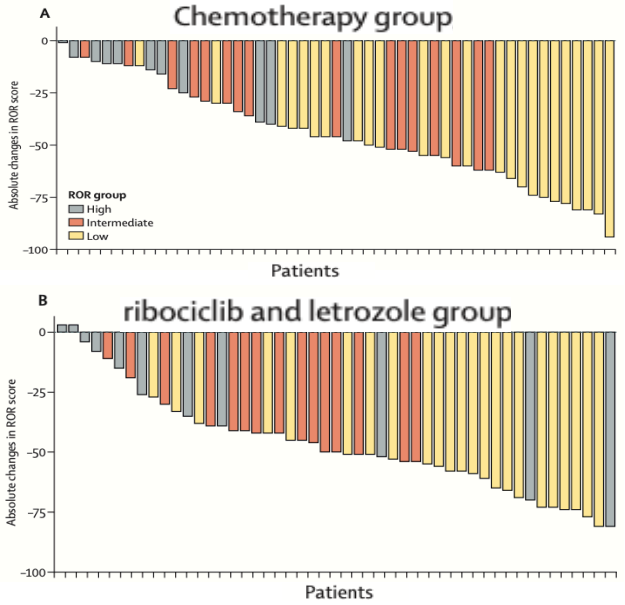
veracyte

CORALLEEN Study –
Change in ROR score after neoadjuvant treatment

Proportion of patients with low-ROR disease after neoadjuvant treatment according to the standard PAM50

	Ribociclib and letrozole group (n=49)		Chemotherapy group (n=52)	
	n (%)	95% CI	n (%)	95% CI
Primary endpoint				
ROR groups				
Low	23 (46·9%)	32·5–61·7	24 (46·1%)	32·9–61·5
Intermediate	15 (30·6%)	18·2–45·4	16 (30·8%)	19·1–45·9
High	11 (22·5%)	11·8–36·7	11 (21·2%)	11·2–35·2
Missing	0	NA	1 (1·9%)	NA

Absolute changes in ROR score between baseline and surgery



Prat A *et al*. Lancet Oncol. 2020 Jan;21(1):33-43

prosigna® Breast cancer gene signature assay

veracyte

Future directions on Prosigna/PAM50 clinical utility

HER2-enriched subtype as a predictor of pCR following traztuzumab and lapatinib without chemotherapy in early-stage HER2+ breast cancer (PAMELA)

Patient Baseline Characteristics

	All patients (n=151)	HER2-enriched (n=101)	Non-HER2-enriched (n=50)
Tumour stage			
T1	60 (40%)	42 (42%)	18 (36%)
T2	79 (52%)	52 (51%)	27 (54%)
T3	12 (8%)	7 (7%)	5 (10%)
p value	0.60	..	..
Histological grade			
Grade 1	23 (15%)	19 (19%)	4 (8%)
Grade 2	27 (18%)	17 (17%)	10 (20%)
Grade 3	101 (67%)	65 (64%)	36 (72%)
p value	0.37	..	..
Histological type			
Ductal	130 (86%)	90 (89%)	40 (80%)
Others*	21 (14%)	11 (11%)	10 (20%)
p value	0.14	..	..
Age, years			
Mean (SD)	55 (13)	56 (13)	53 (13)
p value	0.32	..	..
*Include lobular, mixed, apocrine and invasive carcinoma of no special type			

	All patients (n=151)	HER2-enriched (n=101)	Non-HER2-enriched (n=50)
Menopausal status			
Pre-menopausal	61 (40%)	37 (37%)	24 (48%)
Post-menopausal	90 (60%)	64 (63%)	26 (52%)
p value	0.22	..	..
Tumour size, mm			
Median (IQR)	24 (18-34)	23 (17-33)	25 (20-35)
p value	0.38	..	..
Clinical nodal status			
N0	98 (65%)	64 (63%)	34 (68%)
N1	50 (33%)	34 (34%)	16 (32%)
N2	3 (2%)	3 (3%)	0
p value	0.59	..	..
Hormone receptor status			
Negative	74 (49%)	63 (62%)	11 (22%)
Positive	77 (51%)	38 (38%)	39 (78%)
Letrozole	37 (48%)	19 (50%)	18 (46%)
Tamoxifen	40 (52%)	19 (50%)	21 (54%)
p value	<0.0001	..	..

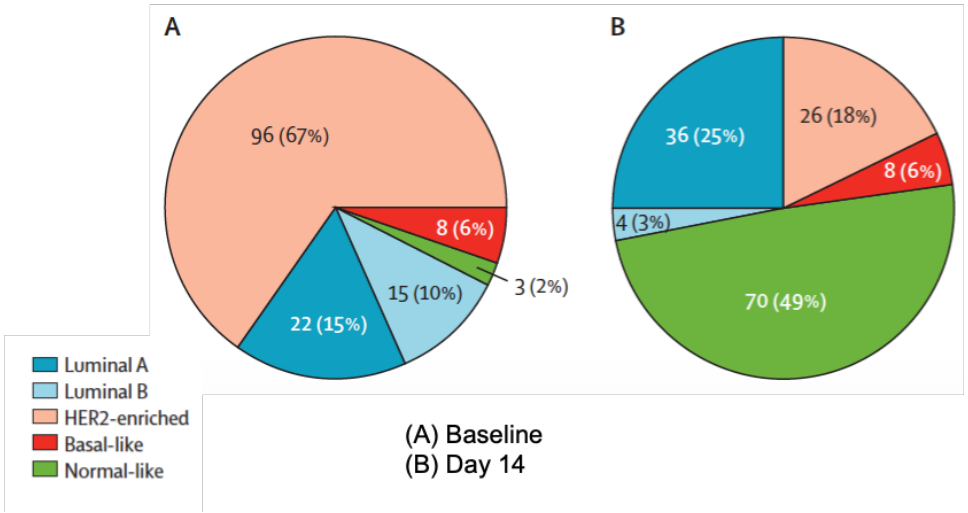
prosigna® Breast cancer gene signature assay

veracyte

Future directions on Prosigna/PAM50 clinical utility –

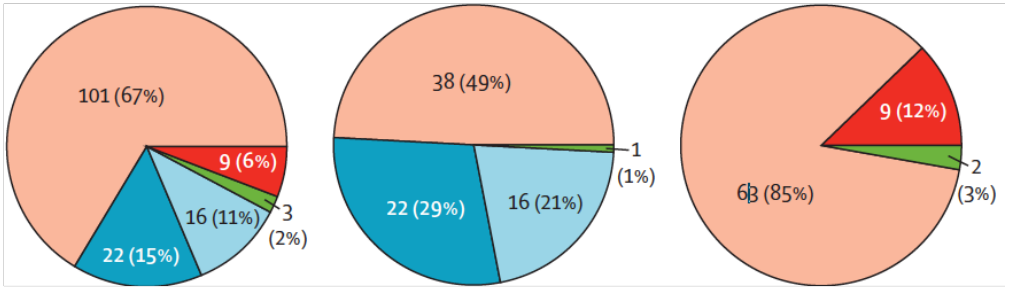
HER2-enriched subtype as a predictor of pCR following traztuzumab and lapatinib without chemotherapy in early-stage HER2+ breast cancer (PAMELA)

Distribution of intrinsic subtypes in patients with paired samples (n=144)



(A) Baseline
(B) Day 14

Distribution of intrinsic subtypes at baseline



(A) All patients (n= 151)
(B) Patients with hormone receptor-positive disease (n=77)
(C) Patients with hormone repector-negative disease (n=74)

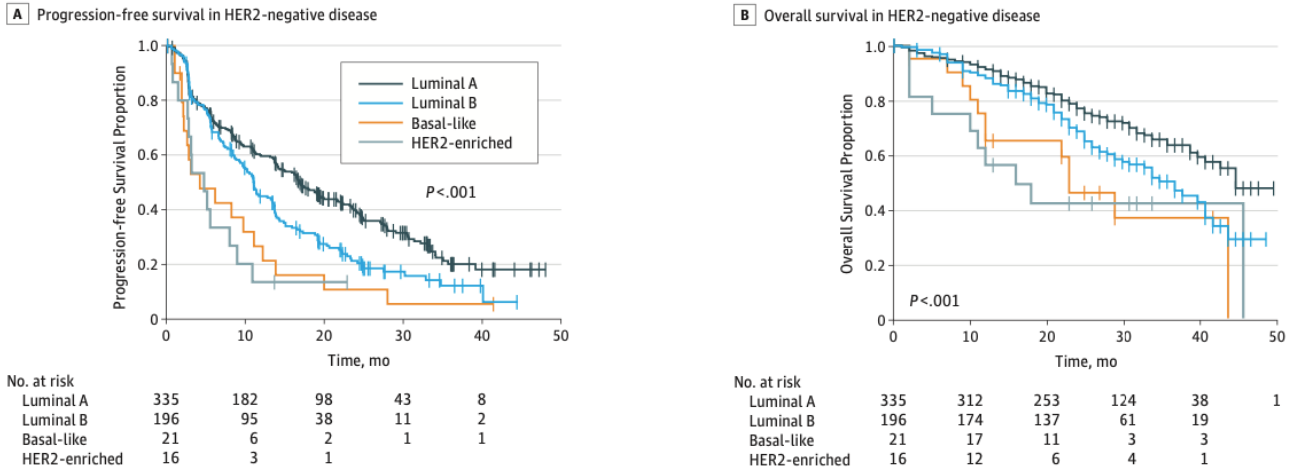
Llombart-Cussac A *et al.* Lancet Oncol. 2017 Apr;18(4):545-554

prosigna® Breast cancer gene signature assay

veracyte

Future directions on PAM50 clinical utility – Metastatic Setting

Prognostic Value of Intrinsic Subtypes in HR+ Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib (EGF30008 phase 3 clinical trial - NCT00073528)

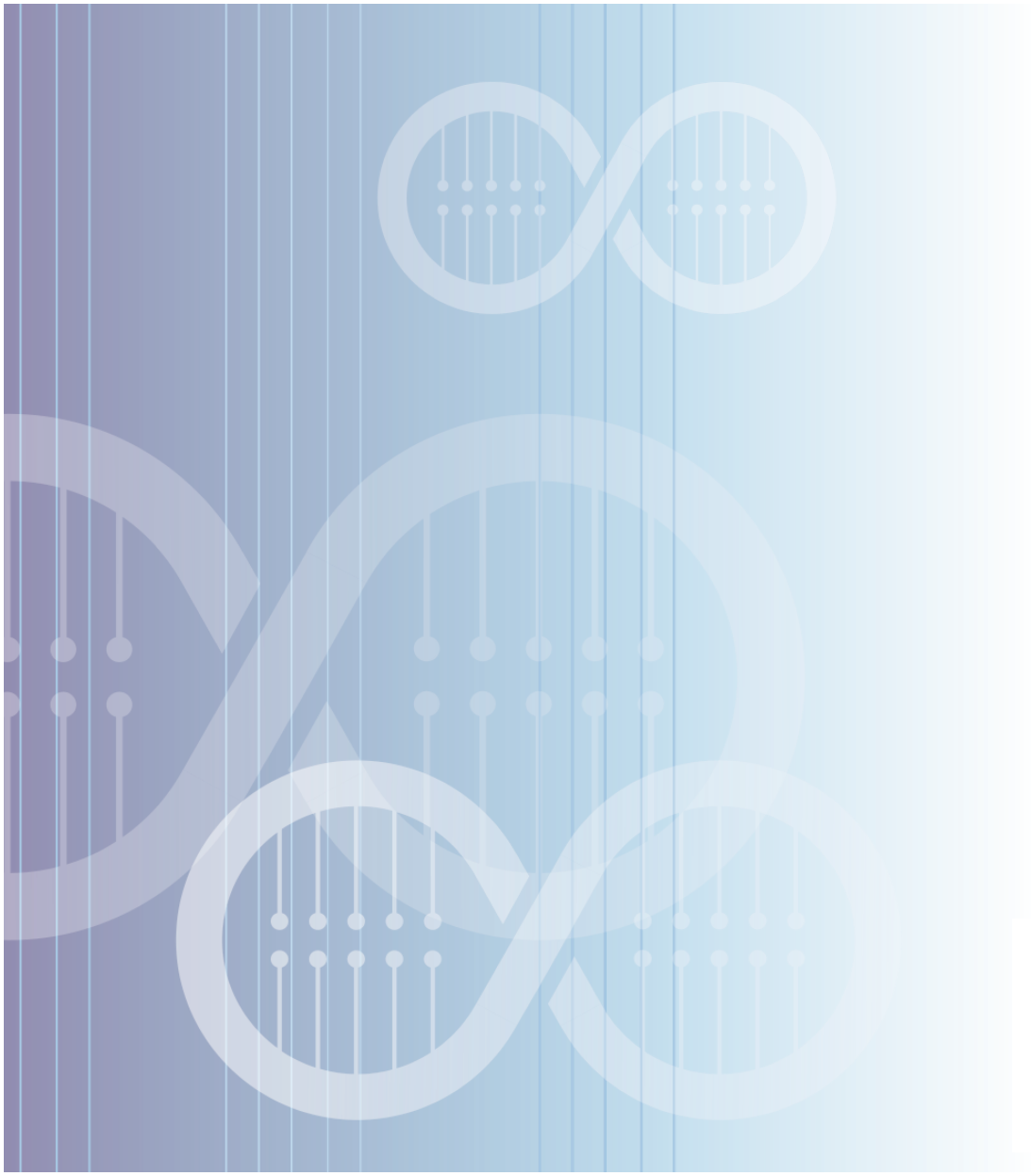


PAM50 and Survival in First-line HR+/HER2-neg Metastatic Breast Cancer

Prat A. *et al.* JAMA Oncol. 2016 Oct 1;2(10):1287-1294

prosigna® Breast cancer gene signature assay

veracyte



procure

PROSIGNA CLINICAL UTILITY REVISION

Consensus about the utility of different breast cancer multigene signatures in early breast cancer in routine clinical practice

veracyte

Objectives of the project

General objective

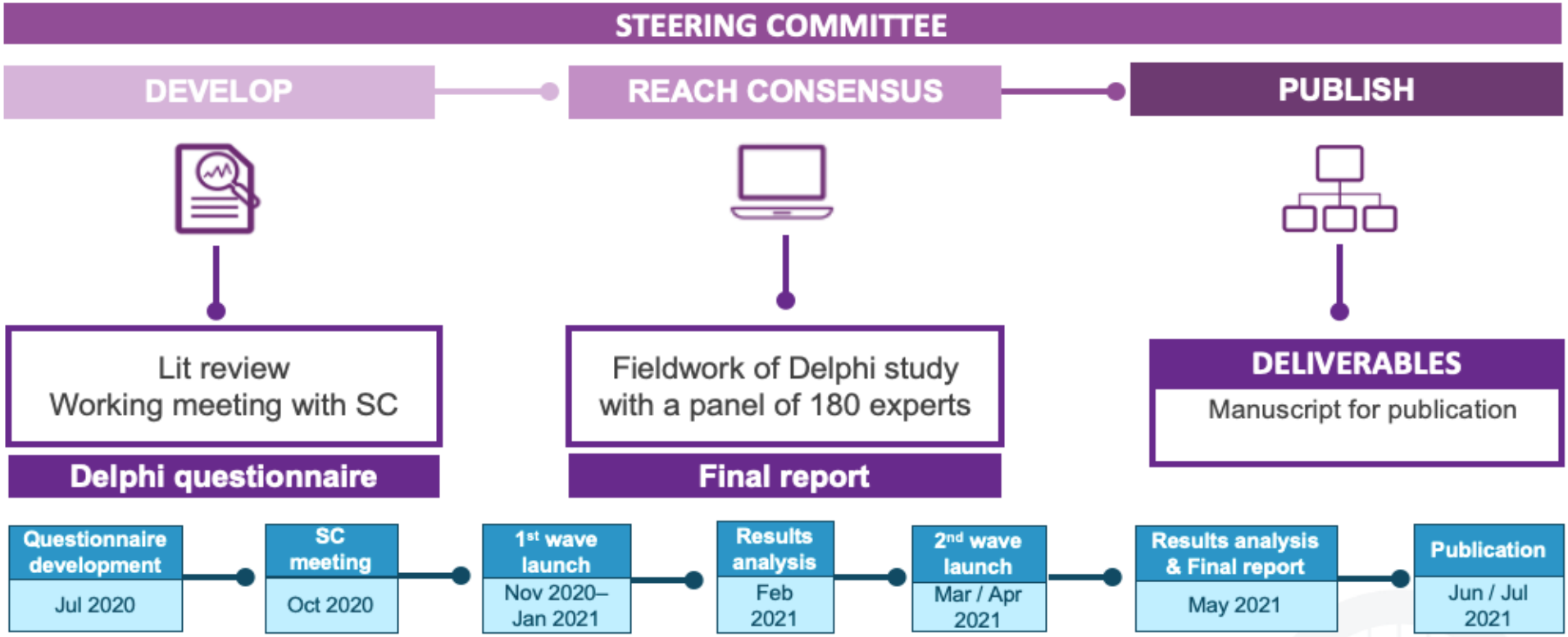
To develop a consensus document about the utility of different breast cancer multigene signatures in early breast cancer in routine clinical practice

Specific objectives

- To comprehensively evaluate the existing evidence supporting the use of breast cancer multigene signatures and the added value that clinicians attribute to them.
- To assess the current and optimized use of breast cancer multigene signatures in patients with differing clinical-pathological profiles.
- To establish recommendations on the use of breast cancer multigene signatures in routine clinical practice.
- To discuss future clinical applications and research opportunities to facilitate a precision medicine approach utilizing breast cancer multigene signatures.

procure
PROSIGNA CLINICAL UTILITY REVISION

PROJECT SCHEME



Conclusions:

1. Prosigna/PAM50 stratifies risk in the adjuvant setting across clinical-pathological subsets
2. Risk stratification will be key in the future landscape of EBC (role of CDK 4/6 inhibitors)
3. Escalation and de-escalation of treatment
4. Potential role in the metastatic setting for better treatment selection